

REMARKS

Applicants' attorney thanks the Examiner for the helpful telephonic interview of March 1, 2005.

Claim Amendments

Claims 3 and 8 have been amended to clarify antecedent basis for the transparent laminate material.

Claims 4 and 5 have been amended to agree with the preamble of Claim 1. In particular, Claims 4(a) has been amended to recite "packaged" deoxygenated hemoglobin blood substitute in and Claims 5 and 4(b) have been amended to recite "packaged deoxygenated" hemoglobin blood substitute.

Claim 7 has been amended to clarify antecedent basis. In particular, Claim 7 has been amended to remove the term "first."

No new matter has been added.

Declarations of Robert A. Houtchens, Ph.D.

In U.S. Serial No. 09/348,881, to which this application claims priority as a continuation, Robert A. Houtchens, Ph.D., Associate Director, Process Development, of Research and Development at Biopure Corporation made a Declaration and a Supplemental Declaration under 37 CFR § 1.132. Copies of the original Declarations are enclosed with this Amendment. In the Supplemental Declaration, Dr. Houtchens stated that one of ordinary skill in the art would not expect to be able to maintain substantially the deoxygenated state of a hemoglobin blood substitute within an oxygen barrier film overwrap, wherein the oxygen barrier film overwrap includes a transparent laminate material that includes an ethylene vinyl alcohol layer and has an oxygen permeability of less than about 0.01 cubic centimeters per 100 square inches over 24 hours at 1 atmosphere and at room temperature. Dr. Houtchens stated that the results were unexpected in part because of the high affinity between deoxygenated hemoglobin and oxygen gas. Dr. Houtchens stated that, because of the relatively high affinity of deoxygenated hemoglobin for oxygen, containment of the deoxygenated hemoglobin within a transparent

overwrap that includes an ethylene vinyl alcohol layer as an oxygen barrier would cause the oxygen gradient across the transparent laminate overwrap to be maintained at a high level over an extended period of time, relative to other liquids, such as water, that do not exhibit the same affinity for oxygen.

Dr. Houtchens stated that, because of a relatively high affinity of deoxygenated hemoglobin for oxygen, the volume of oxygen that would permeate a transparent laminate material employed as an overwrap for deoxygenated hemoglobin would be expected by one of ordinary skill in the art to be significantly greater than the amount of oxygen that would be expected to be transported across the same laminate when employed as an overwrap for another liquid, such as water, that did not exhibit the same affinity for oxygen as deoxygenated hemoglobin. Therefore, according to Dr. Houtchens, the demonstrated stability of Applicants' claimed preserved deoxygenated hemoglobin blood substitute would not be expected from the observed oxygen permeability of ethylene vinyl alcohol because, *inter alia*, deoxygenated hemoglobin has an affinity for oxygen that would maintain an oxygen gradient across the laminate over an extended period of time that is relatively high, as compared to other liquids, such as water, that do not exhibit the same affinity for oxygen.

Dr. Houtchens stated that it was his opinion that one of ordinary skill in the art would not expect to see the low amounts of methemoglobin measured in the deoxygenated hemoglobin blood substitute stored in the manner described in Example 4 of the specification because of a relatively high affinity of deoxygenated hemoglobin for oxygen. Despite the known oxygen permeability of ethylene vinyl alcohol, one of ordinary skill in the art would not expect to be able to maintain substantially the deoxygenated state of a hemoglobin blood substitute by containing the deoxygenated hemoglobin blood substitute within an oxygen barrier film overwrap, wherein the oxygen barrier film overwrap comprises a transparent laminate material that includes an ethylene vinyl alcohol layer and has an oxygen permeability of less than about 0.01 cubic centimeters per 100 square inches over 24 hours at 1 atmosphere and at room temperature. Further, according to Dr. Houtchens, the results obtained by Applicants' would not be expected in view of the teachings of Nho, *et al.*, or Dodrill, (or Hong, *et al.*, which was not cited in the current Office Action) taken separately or in combination, because, *inter alia*, the references fail

to disclose or suggest use of ethylene vinyl alcohol as an oxygen barrier in the transparent laminate material overwrapping a deoxygenated hemoglobin blood substitute.

Rejection of Claims under 35 U.S.C. § 103(a)

Claims 6 and 8-9 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Nho, *et al.* (U.S. Patent No. 5,234,903) in view of Dodrill (Barrier Coated Polyester Films for Healthcare Packaging). The Examiner stated that Nho, *et al.* teach a method of obtaining a deoxygenated hemoglobin solution that may be utilized as a safe and effective red blood substitute in humans as well as animals citing column 13, line 38-40.¹ The Examiner agrees that Nho, *et al.* do not teach the specifics of the container as claimed.² The Examiner stated that Dodrill teaches that polyvinyl alcohol coted OPET film “significantly improves the oxygen barrier properties when the relative humidity is below 50%.”³ The Examiner stated that Dodrill teaches that PVOH coated OPET film composites can be used for products that require good oxygen barrier properties and that silicon oxide coated OPET provides an excellent oxygen and moisture barrier properties.⁴ The Examiner stated that it would have been obvious to one of ordinary skill in the art at the time the invention was made to make a blood substitute according to Nho, *et al.* and store the blood substitute in a container as disclosed by (Dodrill) because “the bags would keep the hemoglobin in the deoxy-state, due to the low oxygen permeability of the films, and thereby increasing the storage life of ready to use hemoglobin.”⁵

Claim 6 is drawn to a preserved deoxygenated hemoglobin blood substitute. The preserved deoxygenated blood substitute of Claim 6 comprises a packaged deoxygenated hemoglobin blood substitute and an oxygen barrier film overwrap package. The oxygen barrier layer of the overwrap package includes ethylene vinyl alcohol (EVOH), and the laminate has an

¹Office Action dated October 1, 2004, page 2.

²Office Action dated October 1, 2004, page 3.

³*Id.*

⁴*Id.*

⁵*Id.*

oxygen permeability of less than about 0.01 cubic centimeters per 645 square centimeters over 24 hours at one atmosphere and at about 23°C. The packaged deoxygenated hemoglobin blood substitute is sealed within the overwrap package. Claim 8 is drawn to an embodiment wherein at least one sheet of the overwrap package comprises said transparent laminate material and wherein at least one other sheet of the overwrap comprises a foil laminate material. Claim 9 is drawn to an embodiment wherein the overwrap package is produced by forming said foil laminate to define at least one chamber, placing the packaged deoxygenated hemoglobin blood substitute into said chamber, and heat sealing the transparent laminate to the foil laminate, whereby said oxygen barrier film overwrap is formed, thereby containing the packaged hemoglobin blood substitute within the overwrap.

Nho, *et al.* describe a chemically modified hemoglobin conjugated to a polyalkylene oxide and storage of said hemoglobin in gas-impermeable bags at 4° C.⁶ Nho, *et al.* teach that the blood substitute is stable at 37° C for only short periods of time.⁷

Dodrill describes barrier-coated, oriented polyester (OPET) films for health care packaging.⁸ The polyester films of Dodrill can be coated, for example, with polyvinyl alcohol (PVOH) or silicon oxide in order to reduce gas permeability.⁹ Dodrill describes the use of polyvinylidene chloride copolymer (PVdC), PVOH, aluminum oxide (Al₂O₃), silicon oxide (SiOx), metalized OPET (Met) or foil OPET (Foil) to provide improved oxygen barrier properties.¹⁰

The combination of Nho, *et al.* and Dodrill fails to disclose or suggest every element of the claimed invention. There is no disclosure or suggestion in either reference, taken separately or in combination, of using an oxygen barrier film overwrap comprising EVOH to preserve a deoxygenated hemoglobin blood substitute. Neither reference even mentions EVOH. In

⁶Nho, *et al.*, Col. 7, lines 39-45; and Col. 16, lines 14-16.

⁷*Id.*, Col. 17, lines 49-56.

⁸Dodrill, page 2, third paragraph.

⁹Dodrill, pages 5, 6, and 8-10.

¹⁰Dodrill, page 16, Table II.

addition, the combination fails to disclose or suggest the preserved deoxygenated blood substitute of Claim 8, wherein the oxygen barrier film overwrap package comprises at least two sheets of laminate material, at least one sheet comprising an oxygen barrier layer that comprises EVOH and at least one other sheet comprising a foil laminate material. Furthermore, the combination fails to disclose or suggest a preserved deoxygenated blood substitute of Claim 9, wherein the overwrap package is produced by forming a foil laminate to define at least one chamber, placing the packaged deoxygenated hemoglobin blood substitute into said chamber and sealing the transparent laminate to the foil laminate, whereby said oxygen barrier film overwrap is formed. Therefore, Claims 6, 8, and 9 are patentable over Nho, *et al.* and Dodrill because the combined teachings of Nho, *et al.* and Dodrill fails to disclose or suggest all of the claim limitations.¹¹

There is no motivation of incentive to modify and combine the teachings of the references to produce Applicants' claimed invention. As discussed above, neither reference even mentions EVOH. In addition, Robert A. Houtchens, Ph.D., who is a named inventor of the instant application, stated in the attached Declaration that one of ordinary skill in the art would not expect that an oxygen barrier film laminate that includes an ethylene vinyl alcohol layer, as employed in the overwrap layer of Example 4, would limit the percent methemoglobin to the level observed following storage over a period of twelve months under the conditions described. Further, Dr. Houtchens stated that one of ordinary skill in the art would not be motivated by the teachings of Nho, *et al.* or Dodrill (or Hong, *et al.* not cited in the current Office Action), taken either separately or in combination, to employ an oxygen barrier film overwrap to package a deoxygenated hemoglobin blood substitute contained within a primary package, wherein the oxygen barrier film overwrap comprises an oxygen barrier layer that includes ethylene vinyl alcohol. Specifically, Dr. Houtchens stated in the Declaration that the permeability to oxygen observed under the conditions described in Example 4, as evidenced by the percent methemoglobin found in the deoxygenated hemoglobin solution after twelve months of storage under the conditions set forth, would be unexpected to one of ordinary skill in the art of blood or blood substitute packaging.

¹¹MPEP at 2143.

Furthermore, Dr. Houtchens stated in the enclosed Supplemental Declaration that one of ordinary skill in the art would not expect, in view of Nho, *et al.*, or Dodrill (or Hong, *et al.* not cited in the current Office Action), taken either separately or in combination, to be able to preserve deoxygenated hemoglobin within an oxygen barrier film overwrap that includes a transparent laminate material having an oxygen barrier layer that includes EVOH, wherein the oxygen permeability of the laminate material is less than about 0.01 cubic centimeters per 100 square inches over 24 hours at 1 atmosphere, at room temperature, and at 0% relative humidity.

There is no motivation or incentive to substitute the gas impermeable bags of Nho, *et al.* with the materials of Dodrill to produce Applicants' claimed invention. Therefore, Applicants' claimed preserved deoxygenated hemoglobin blood substitute is non-obvious in view of Nho, *et al.* or Dodrill, separately or in combination, under 35 U.S.C. §103. Withdrawal and reconsideration of the rejection are respectfully requested.

Rejection of Claims under 35 U.S.C. § 103(a)

Claim 7 is rejected under 35 U.S.C. 103(a) as being unpatentable over Nho, *et al.* in view of Dodrill as applied to Claims 6, 8-9 above, and further in view of Akkapeddi, *et al.* or Galli.

The Examiner stated that "[t]he difference between the prior art and the instant application is that the reference does not teach the coextruding of the medium density layer, such as polypropylene or polyethylene and the oxygen barrier layer, such as ethylene vinyl alcohol," citing Akkapeddi, *et al.* and Galli.

The teachings of Nho, *et al.* and Dodrill are described above. There is no disclosure or suggestion in Nho, *et al.* or Dodrill, taken either separately or in combination, of use of a transparent laminate having the oxygen permeability of the laminates employed by Applicants' claimed invention. In addition, there is no disclosure or suggestion in Nho, *et al.* or Dodrill, taken either separately or in combination, of a transparent laminate material that employs EVOH as an oxygen barrier, wherein the transparent laminate material has the oxygen permeability of the transparent laminate material employed in Applicants' claimed invention. Furthermore, as described above, Dr. Houtchens stated in the enclosed Supplemental Declaration that one of ordinary skill in the art would not expect, in view of Nho, *et al.*, Dodrill (or Hong, *et al.* not cited in the current Office Action), taken either separately or in combination, to be able to preserve

deoxygenated hemoglobin within an oxygen barrier film overwrap that includes a transparent laminate material having an EVOH, wherein the oxygen permeability of the laminate material is less than about 0.01 cubic centimeters per 100 square inches over 24 hours at 1 atmosphere, at room temperature, and at 0% relative humidity.

Thus, there is no motivation or incentive to substitute the gas impermeable bags of Nho, *et al.* with the materials of Dodrill to produce Applicants' claimed invention.

Neither Akkapeddi, *et al.* nor Galli remedy the deficiencies of Nho, *et al.* or Dodrill, taken either separately or in combination. For example, as with Nho, *et al.* and Dodrill, there is no disclosure or suggestion of employing an oxygen barrier film overwrap to preserve a deoxygenated hemoglobin blood substitute contained in a primary package, wherein the oxygen barrier film overwrap employs an ethylene vinyl alcohol layer. Furthermore, neither reference, taken either separately or in combination, discloses or suggests use of the coextruded material in an oxygen barrier film overwrap to a deoxygenated hemoglobin blood substitute contained within a primary package, as is claimed by Applicants. There is no disclosure of any material that has the oxygen permeability of the oxygen barrier film overwrap employed in Applicants' claimed invention. Therefore, Claim 7 is non-obvious over Nho, *et al.* in view of Dodrill, and further in view of Akkapeddi, *et al.* or Galli. Withdrawal and reconsideration of the rejection are respectfully requested.

Double Patenting


Claims 1-9 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 1-15 of U.S. Patent No. 6,271,351. Claims 1-9 are also rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 1-9 of U.S. Patent No. US 6,288,027. A Terminal Disclaimer over U.S. Patent No. 6,271,351 and U.S. Patent No. 6,288,027 is being filed concurrently herewith.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

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Dated: *April 1, 2005*